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(54) Triazole antifungal agents.

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EP-A-0 054 974

K.H. Büchal, Pflanzenschutz und Schädlingsbekämpfung, Georg Thieme Verlag, Stuttgart 1977, Seite 152, "Carbendazim", "Benomyl"

The file contains technical information submitted after the application was filed and not included in this specification

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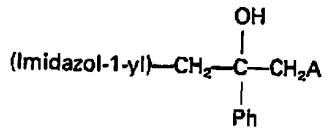
Description

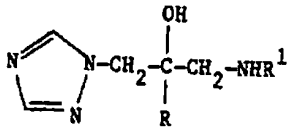
This invention relates to 1,2,4-triazole derivatives which have antifungal activity and are useful in the treatment of fungal infections in animals, including humans, and as agricultural fungicides.

EP—A—0054974 discloses imidazolyl antifungal agents of the formula:



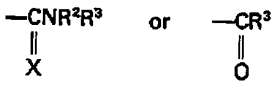
where A is, for example, $—NR^3R^4$ where R^3 and R^4 are various stated substituents such as C_1—C_4 alkyl, C_3—C_6 cycloalkyl and benzyl etc., and Ph is phenyl optionally substituted with halogen.

According to the invention, there are provided compounds of the formula:



— (I)

and their O-esters and O-ethers, as hereinafter defined; wherein R is naphthyl, biphenylyl or phenyl optionally substituted by 1 to 3 substituents each independently selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy; and R^1 is



where

X is O or S;

R^2 is hydrogen or C_1—C_4 alkyl; and

R^3 is hydrogen, C_1—C_4 alkyl, C_3—C_6 cycloalkyl, aryl, aralkyl, or heteroaryl, said aryl, aralkyl and heteroaryl groups being as hereinafter defined; or

R^2 and R^3 taken together with the N atom to which they are attached represent a 1-pyrrolidinyl or piperidino group;

and the pharmaceutically and agriculturally acceptable salts thereof.

The O-ethers of the alcohols of the formula (I) are the C_1—C_8 alkyl, C_2—C_4 alkenyl, C_2—C_4 alkynyl, phenyl and benzyl ethers, the benzyl ethers being optionally ring substituted by halo, C_1—C_4 alkyl or C_1—C_4 alkoxy.

The O-esters of the alcohols of the formula (I) are the C_2—C_4 alkanoyl or benzoyl esters, the benzoyl esters being optionally substituted by halo, C_1—C_4 alkyl or C_1—C_4 alkoxy.

The preferred ester is the acetyl ester.

R is preferably phenyl substituted by 1 or 2 substituents selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy, most preferably 1 or 2 substituents selected from halo and CF_3.

R is in particular 2,4-difluorophenyl or 2,4-dichlorophenyl.

"Halo" means F, Cl, Br or I.

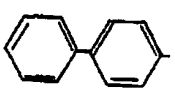
Where appropriate, alkyl and alkoxy groups can be straight or branched chain.

"Aryl" means phenyl optionally substituted by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy.

"Aralkyl" means benzyl optionally substituted on the phenyl ring portion by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy.

"Heteroaryl" means pyridyl, pyrimidinyl or pyrazinyl all optionally substituted by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl, C_1—C_4 alkoxy and hydroxy.

The preferred biphenylyl group is



The invention also provides a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt, O-ester or O-ether (as hereinbefore defined) thereof, together with a

pharmaceutically acceptable diluent or carrier. The composition is preferably for human use and in tablet, capsule, injectable or ointment form.

The invention further provides a compound of the formula (I) or a pharmaceutically acceptable salt, O-ester or O-ether (as hereinbefore defined) thereof, for use in treating fungal infections in humans.

The invention yet further provides a plant or seed antifungal composition comprising a compound of the formula (I) or an agriculturally acceptable salt thereof, together with an agriculturally acceptable diluent or carrier.

The invention yet further provides a method of treating a plant or seed having a fungal infection, which comprises treating said plant or seed with an effective amount of a compound of the formula (I) or with an agriculturally acceptable salt thereof.

The compounds of the formula (I) and their salts, O-esters and O-ethers are very active antifungal agents, useful in combating fungal infections in animals, including humans. For example they are useful in treating topical fungal infections in man caused by, among other organisms, species of *Candida*, *Trichophyton*, *Microsporum*, or *Epidermophyton*, or in mucosal infections caused by *Candida albicans* (e.g. thrush and vaginal candidiasis). They may also be used in the treatment of systemic fungal infections caused by, for example, *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Coccidioides*, *Paracoccidioides*, *Histoplasma* or *Blastomyces*.

The *in vitro* evaluation of the antifungal activity of the compounds can be performed by determining the minimum inhibitory concentration (m.i.c.) which is the concentration of the test compound in a suitable medium at which growth of the particular micro-organism fails to occur. In practice, a series of agar plates, each having the test compound incorporated at a particular concentration are inoculated with a standard culture of, for example, *Candida albicans* and each plate is then incubated for 48 hours at 37°C. The plates are then examined for the presence or absence of growth of the fungus and the appropriate m.i.c. value is noted. Other micro-organisms used in such tests can include *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Trichophyton* spp., *Microsporum* spp, *Epidermophyton floccosum*, *Coccidioides immitis*, and *Torulopsis glabrata*.

The *in vivo* evaluation of the compounds can be carried out at a series of dose levels by intraperitoneal or intravenous injection or by oral administration, to mice which are inoculated with a strain of *Candida albicans*. Untreated mice die within 48 hours and the dose level at which the compound provides 50% protection against the lethal effect of the infection is noted.

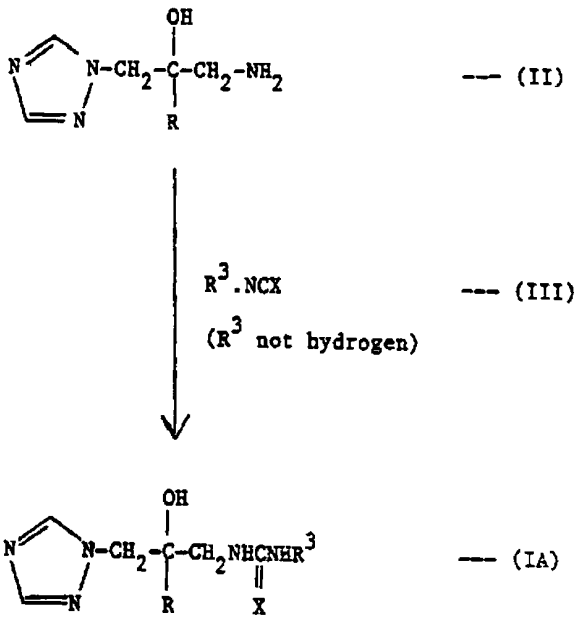
For human use, the antifungal compounds of the formula (I) (or salts, esters or ethers thereof) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic.

For oral and parenteral administration to human patients, it is expected that the daily dosage level of the antifungal compounds of the formula (I) will be from 0.1 to 6 mg/kg (in divided doses) when administered by either the oral or parenteral route. Thus tablets or capsules of the compounds can be expected to contain from 5 mg to 0.5 g of active compound for administration singly or two or more at a time as appropriate. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Alternatively, the antifungal compounds of the formula (I) may be administered in the form of a suppository or pessary, or may be applied topically in the form of a lotion, solution, ointment or dusting powder. For example, they may be incorporated into an ointment consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin; or they may be incorporated, at a concentration of between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

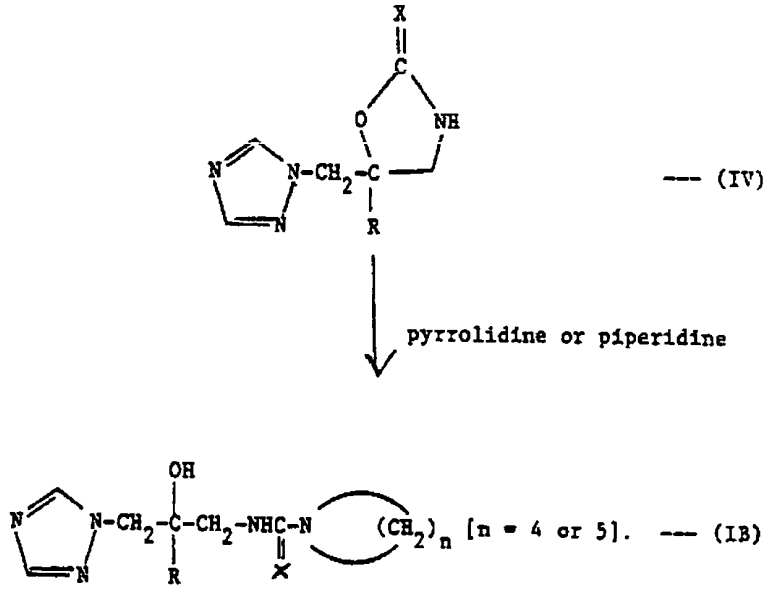
The ureas and thioureas of the formula (I) can be prepared by the following general methods:

(1)



The reaction is typically carried out in a suitable organic solvent, e.g. dichloromethane, at a temperature of from 0—30°C for up to about 24 hours. Generally a slight excess of (III) is used. The solution can then be evaporated and the residue purified by conventional procedures, e.g. by recrystallisation or chromatography.

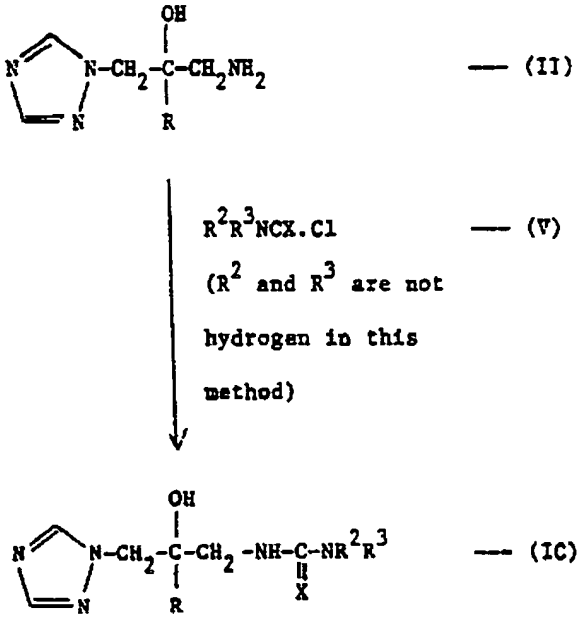
(2)



(X = O or S)

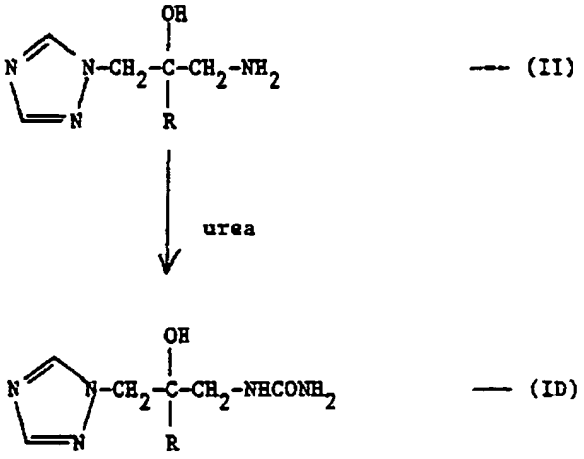
The reaction is typically carried out by heating the 1,3-oxazolidin-2-one or 1,3-oxazolidin-2-thione derivative (IV) with an excess of the appropriate amine either without a solvent or in a suitable organic solvent, e.g. dioxan, for up to about 24 hours. Temperatures up to reflux can be used. The solvent is then evaporated and the residue purified by standard procedures.

(3).



In a typical procedure the amine (II) is dissolved in a suitable organic solvent, e.g. pyridine, with stirring and cooling. The carbamoyl or thiocarbamoyl chloride (V) is then added, generally in a slight excess, and the mixture stirred for up to about 18 hours. Water is then added and the mixture is extracted with a suitable organic solvent, e.g. dichloromethane. The product may be recovered from the organic phase by standard procedures.

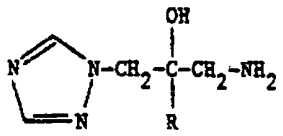
(4)



The reaction is preferably carried out under reflux in aqueous acidic conditions for up to about 12 hours, the product again being recovered by standard procedures.

The acylamino derivatives of the formula (I) may be prepared by the following routes:

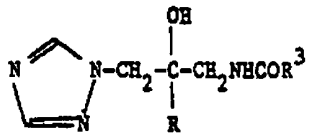
(1)



--- (II)

R^3COOH/1,1'-carbonyldiimidazole,

R^3COCl or $(R^3CO)_2O$ [R^3 not hydrogen].

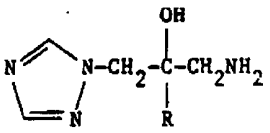


--- (IE)

When the free acid is used, the reaction is typically carried out by heating the acid (generally in slight excess), amine (II) and 1,1'-carbonyldiimidazole at up to reflux temperature in a suitable organic solvent, e.g. dry tetrahydrofuran (THF), for up to about 6 hours. The solvent is then evaporated and the product may be recovered from the residue and purified by conventional procedures.

When using an acid chloride or anhydride, heating is not generally necessary. Typically the acid chloride or anhydride and amine (II) are stirred in a suitable organic solvent, e.g. dry pyridine, at 0—5°C for a few hours, typically 1—2 hours. Water is then added and the mixture is extracted with a suitable organic solvent, e.g. dichloromethane. The product may then be recovered from the organic phase and purified by conventional procedures.

(2)

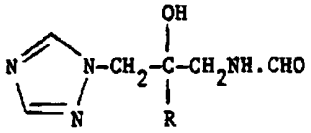


--- (II)

Formylating agent

(e.g. a C_1-C_4 alkyl

formate)



--- (IF)

The preferred formylating agent is ethyl formate.

Typically the amine (II) and ethyl formate (generally in excess) are heated together under reflux for a few hours. The product can then be recovered and purified by conventional procedures.

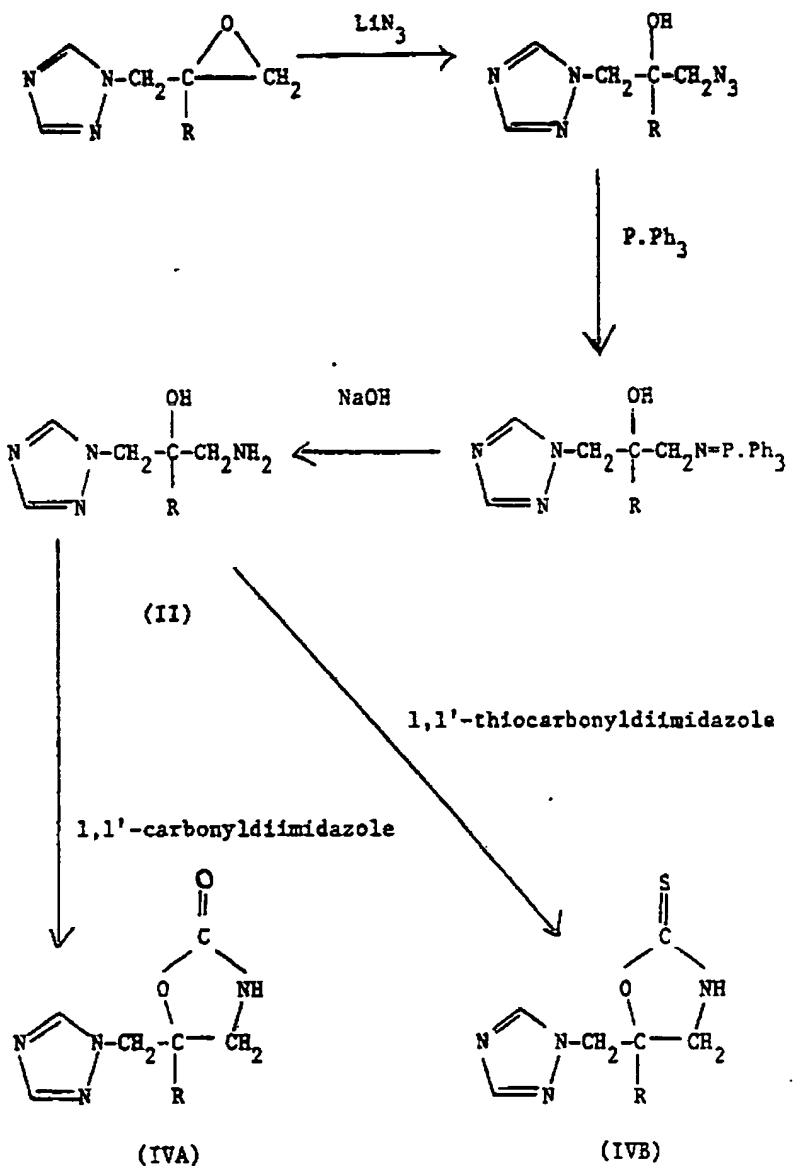
Other conventional formylating agents such as formic acid/acetic anhydride and dimethyl formamide/sodium methoxide, can also be used.

The O-ethers can be made by conventional methods, e.g. by treating an alkali metal salt of the alcohols of the formula (I), e.g. a lithium or sodium salt, with the appropriate halide, i.e. a C_1—C_6 alkyl, C_2—C_4 alkenyl, C_2—C_4 alkynyl, phenyl or benzyl halide. O-Esters can also be made conventionally, e.g. by treating an alkali metal salt of compound (I) with an appropriate acid chloride or anhydride.

The compounds of the invention contain optically active centres, and the invention includes both the resolved and unresolved forms. Resolution can be carried out according to standard techniques.

Pharmaceutically acceptable acid addition salts of the compounds of the formula (I) are generally those formed from strong acids which form non-toxic acid addition salts, such as hydrochloric, hydrobromic, sulphuric, oxalic and methanesulphonic acids. These salts can be obtained conventionally by reaction of the free base with the desired acid in an appropriate organic solvent. The invention also includes the alkali metal and ammonium salts, which again may be formed conventionally.

The starting materials for the previous routes are either known compounds or may be prepared conventionally. Typical routes, which are illustrated in detail in the following Preparations, are as follows:



The compounds of the formula (I) and their salts also have activity against a variety of plant pathogenic fungi, including for example various rusts, mildews and moulds, and the compounds are thus useful for treating plants and seeds to eradicate or prevent such diseases.

The *in vitro* evaluation of the activity of the compounds against plant fungi can be determined by measuring their minimum inhibitory concentrations in the same way as previously described except that the plates are incubated at 30°C for 48 hours or longer before being examined for the presence or absence of growth.

Micro-organisms used in such tests include *Cochliobolus carbonum, Pyricularia oryzae, Glomerella cingulata, Penicillium digitatum, Botrytis cinerea* and *Rhizoctonia solani.*

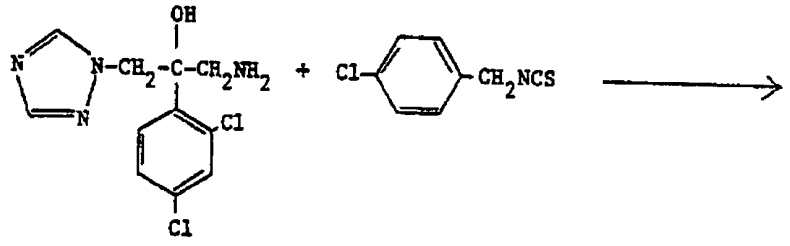
For agricultural and horticultural purposes the compounds and their agriculturally acceptable salts are preferably used in the form of a composition formulated as appropriate to the particular use and purpose desired. Thus the compounds may be applied in the form of dusting powders, or granules, seed dressings, aqueous solutions, dispersions or emulsions, dips, sprays, aerosols or smokes. Compositions may also be supplied in the form of dispersible powders, granules or grains, or concentrates for dilution prior to use. Such compositions may contain such conventional carriers, diluents or adjuvants as are known and acceptable in agriculture and horticulture and they are manufactured in accordance with conventional procedures. The compositions may also incorporate other active ingredients, for example, compounds having herbicidal or insecticidal activity or a further fungicide. The compounds and compositions can be applied in a number of ways, for example they can be applied directly to the plant foliage, stems, branches, seeds or roots or to the soil or other growing medium, and they may be used not only to eradicate disease, but also prophylactically to protect the plants or seeds from attack.

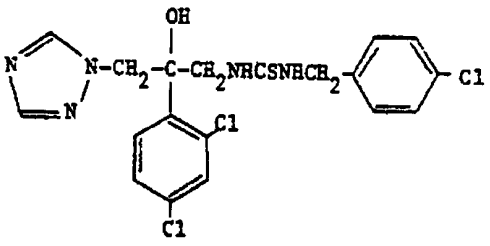
The following Examples illustrate the invention. All temperatures are in °C:

Example 1

Preparation of N-(4-chlorobenzyl)-N'-[2-(2,4-dichlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)prop-1-yl]thiourea

(A)





The amine (A) (0.4 g, 1.39 mmole) and 4-chlorobenzylisothiocyanate (0.28 g, 1.53 mmole) were stirred in dichloromethane (20 ml) and the mixture was cooled in an ice-bath. After 1 hour the ice-bath was removed and stirring was continued for a further 18 hours. Evaporation of solvent and recrystallisation from ethanol gave the *title compoundd*, 0.55 g (84%), m.p. 209—210°.

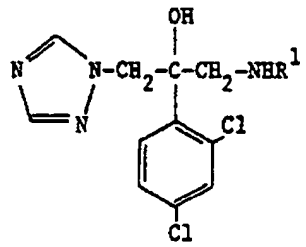
Analysis %:

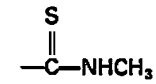
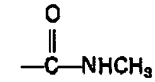
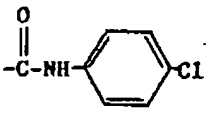
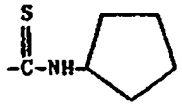
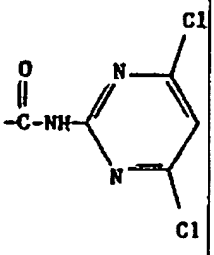
Found: C, 48.48; H, 4.01; N, 15.09;

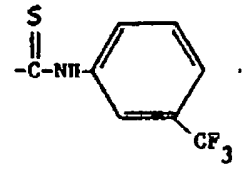
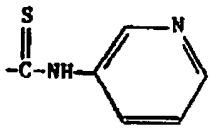
Calculated for $C_{19}H_{18}Cl_3N_5OS$: C, 48.48; H, 3.85; N, 14.88.

Examples 2—8

The following compounds were prepared similarly to Example 1, starting from the same amine and appropriate isocyanate or isothiocyanate:

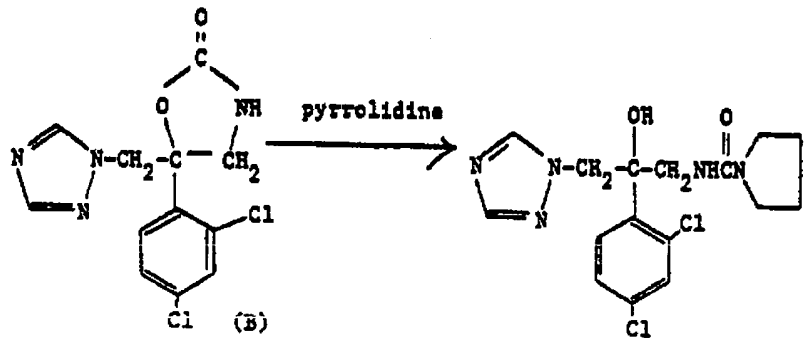


Example No.	R^1	Yield (%)	m.p. (°C)	Analysis % (Calculated in brackets) C	H	N
2		66	207—208	43.41 (43.35	4.26 4.20	19.96 19.44)
3		65	166—168	45.19 (45.36	4.38 4.39	20.5 20.35)
4		55	205—207	49.15 (49.06	3.76 3.66	16.22 15.89)
5		59	196—198	49.13 (49.28	4.97 5.10	16.96 16.90)
6		48	210—212	40.38 (40.28	2.87 2.75	20.78 20.55)

Example No.	R^1	Yield (%)	m.p. (°C)	Analysis % (Calculated in brackets) C	H	N
7		64	195—197	46.62 (46.55	3.32 3.29	14.63 14.28)
8		60	188—190	48.24 (48.24	3.77 3.81	19.99 19.86)

Example 9

Preparation of N-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)prop-1-yl]-N'N'-tetramethyleneurea



(B)

The 1,3-oxazolidin-2-one (B) (0.35 g, 1.12 mmole) and pyrrolidine (0.59 g, 7 mmole) were heated under reflux in dioxan (15 ml) for 18 hours. The solvent was then evaporated and the residue was chromatographed on 230—400 mesh silica, eluting with a mixture of dichloromethane:methanol:0.88 ammonia (98:2:1), to give, after one recrystallisation from ethyl acetate, the *title compound* 0.18 g (42%), m.p. 174—176°.

Analysis %:

Found: C, 49.71; H, 4.94; N, 18.33;

Calculated for $C_{16}H_{19}Cl_2N_5O_2$: C, 50.01; H, 4.98; N, 18.23.

Example 10

N-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)prop-1-yl]-N',N'-tetramethylenethiourea was prepared similarly to the previous Example, starting from the corresponding oxazolidin-2-thione and pyrrolidine. It had an m.p. of 209—210° (33% yield).

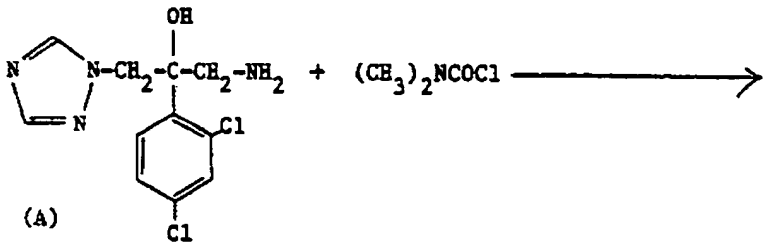
Analysis %:

Found: C, 48.09; H, 4.75; N, 17.87;

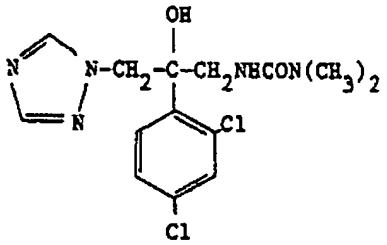
Calculated for $C_{16}H_{19}Cl_2N_5OS$: C, 48.01; H, 4.78; N, 17.50.

Example 11

Preparation of N-[2-(2,4-dichlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)prop-1-yl]-N',N'-dimethylurea



(A)



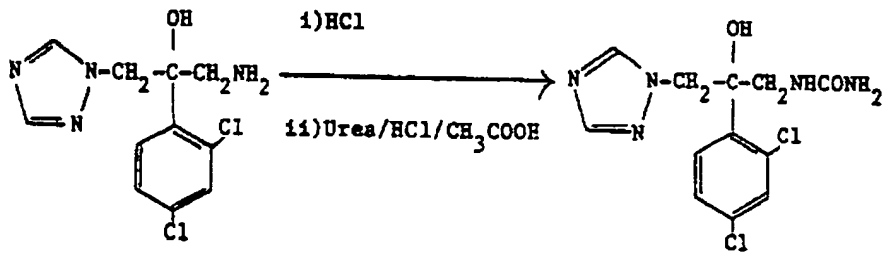
The amine (A) (0.4 g, 1.39 mmole) was dissolved in pyridine (10 ml) and the solution was stirred and cooled in ice. Dimethylcarbamoyl chloride (0.18 g, 1.67 mmole) was then added and stirring was continued for 2 hours. Water (20 ml) was then added and the mixture was extracted three times with dichloromethane (90 ml in all). The combined extracts were dried ($MgSO_4$) and evaporated and the residue was chromatographed on silica (230—400 mesh), eluting with a mixture of dichloromethane:methanol:0.88 ammonia (93:7:1) to give, after one recrystallisation from ethanol, the *title compound*, 0.29 g (58%), m.p. 189—190°.

Analysis %:

Found:	C, 47.07;	H, 4.83;	N, 19.87;
Calculated for $C_{14}H_{17}Cl_2N_5O_2$:	C, 46.94;	H, 4.78;	N, 19.55.

Example 12

Preparation of N-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)prop-1-yl]urea



(A)

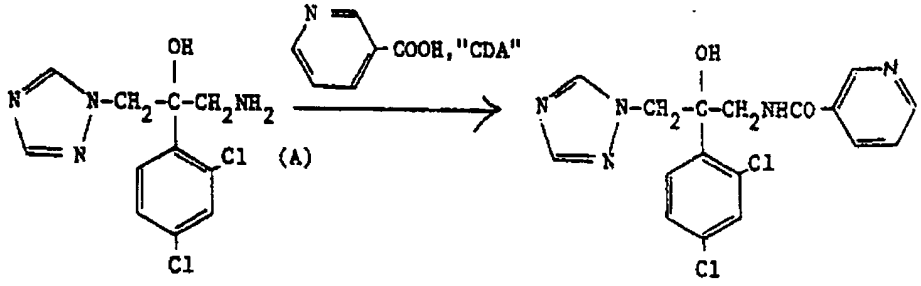
The amine (A) (0.4 g, 1.39 mmole) was dissolved in ether and a solution of hydrogen chloride in ether was added. The solvent was then evaporated and the residue was added to a mixture of urea (0.32 g, 5.3 mmole), water (20 ml), and 24 ml of a mixture of water:concentrated hydrochloric acid: acetic acid (50:1:1). The solution was heated under reflux for 11 hours, allowed to cool and then basified by the addition of solid sodium carbonate. Extraction with ethyl acetate followed by drying ($MgSO_4$) and evaporation of the combined extracts gave a white glassy solid which was chromatographed on silica (230—400 mesh), eluting with a mixture of dichloromethane:methanol:0.88 ammonia (93:7:1), to give after one recrystallisation from ethyl acetate, the *title compound*, 0.19 g (41%), m.p. 168—169°.

Analysis %:

Found:	C, 43.90;	H, 4.01;	N, 21.16;
Calculated for $C_{12}H_{13}Cl_2N_5O_2$:	C, 43.65;	H, 3.97;	N, 21.21.

Example 13

Preparation of N-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-prop-1-yl]-3-pyridinecarboxamide



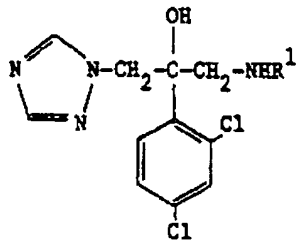
3-Pyridinecarboxylic acid (0.235 g, 1.9 mmole) and 1,1'-carbonyldiimidazole ("CDA") (0.310 g, 1.9 mmole) were dissolved in dry THF (10 ml). A solution of the amine (A) (0.5 g, 1.74 mmole) in THF (20 ml) was then added and the mixture was heated under reflux for 2 hours. The THF was then evaporated and the residue was dissolved in ethyl acetate. The solution was washed with water (2 × 100 ml), dried ($MgSO_4$) and evaporated to give a white glassy solid which was triturated with ether to give, as a white solid, the *title compound*, 0.54 g (81%), m.p. 175°.

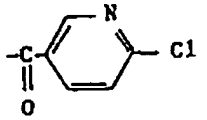
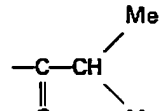
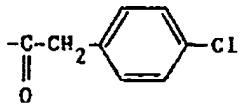
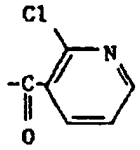
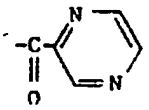
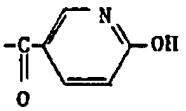
Analysis %:

Found:	C, 51.94;	H, 3.79;	N, 18.08;
Calculated for $C_{17}H_{15}Cl_2N_5O_2$:	C, 52.05;	H, 3.85;	N, 17.85.

Examples 14—19

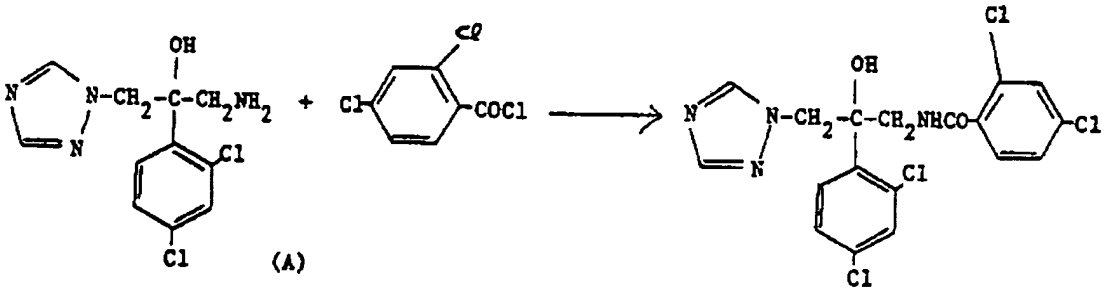
The following compounds were prepared similarly to the previous Example, starting from the same amine, appropriate acid, and "CDA".



Example No.	R^1	Yield (%)	m.p. (°C)	Analysis % (Calculated in brackets) C	H	N
14		81	197—8	48.08 (47.85	3.40 3.30	16.70 16.41)
15		62	154—5	50.37 (50.43	5.07 5.08	15.69 15.68)
16		50	150	51.76 (51.86	3.98 3.89	13.06 12.74)
17		56	139—40	47.61 (47.85	3.33 3.30	17.09 16.41)
18		53	188—9	48.87 (48.86	3.62 3.59	22.08 21.37)
19		55	284 with decomp.	50.08 (50.01	3.79 3.70	17.41 17.15)

Example 20

Preparation of N-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)prop-1-yl]-2,4-dichlorobenzamide



(A)

To a stirred and ice-cooled suspension of the amine (A) (0.4 g, 1.39 mmole) in pyridine (10 ml) was added 2,4-dichlorobenzoyl chloride (0.35 g, 1.67 mmole) and stirring was continued for 1 hour. Water (20 ml) was then added and the mixture was extracted twice with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give a yellow oil which was chromatographed on silica (230—400

mesh), eluting first with ethyl acetate and then with a mixture of ether:ethanol:0.88 ammonia (97:3:1) to give as a white solid, after one recrystallisation from ethyl acetate/60—80° petrol, the *title compound*, 0.413 g (72%), m.p. 153—4°C.

Analysis %:

Found:	C, 46.88;	H, 3.05;	N, 12.55;
Calculated for $C_{18}H_{14}Cl_4N_4O_2$:	C, 46.98;	H, 3.07;	N, 12.18.

Example 21

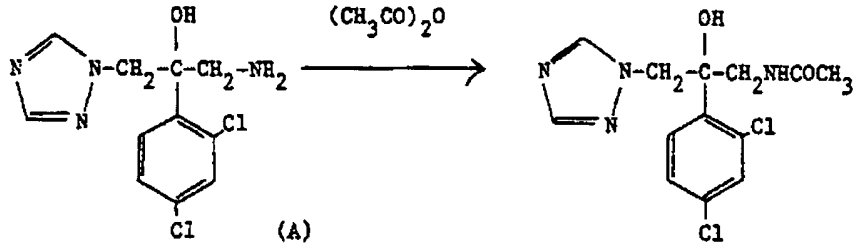
The corresponding 4-chlorobenzamide was prepared similarly to the previous Example, starting from the same amine and 4-chlorobenzoyl chloride. The produce had an m.p. of 199—200° (75% yield).

Analysis %:

Found:	C, 50.96;	H, 3.61;	N, 13.10;
Calculated for $C_{18}H_{15}Cl_3N_4O_2$:	C, 50.79;	H, 3.55;	N, 13.16.

Example 22

Preparation of N-[2-(2,4-dichlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)prop-1-yl]acetamide



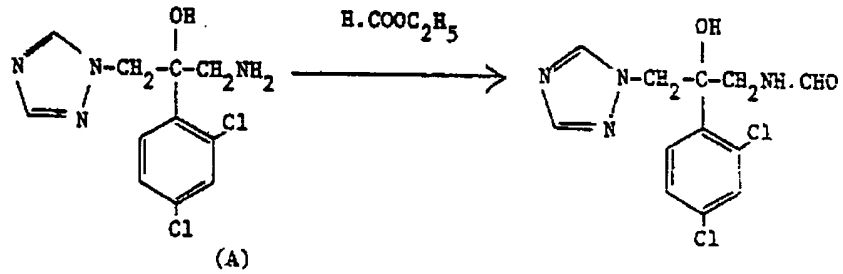
To a stirred and ice-cooled suspension of the amine (A) (0.4 g, 1.39 mmole) in pyridine (10 ml) was added acetic anhydride (0.17 g, 1.67 mmole) and stirring was continued for 2 hours. Water (20 ml) was then added and the mixture was extracted three times with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give a white solid which was recrystallised once from ethyl acetate to give the title compound, 0.27 g (59%), m.p. 178—179°.

Analysis %:

Found:	C, 47.31;	H, 4.23;	N, 17.20;
Calculated for $C_{13}H_{14}Cl_2N_4O_2$:	C, 47.43;	H, 4.29;	N, 17.02.

Example 23

Preparation of N-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)prop-1-yl]formamide



The amine (A) (250 mg) was heated under reflux with excess ethyl formate (10 ml) for 3 hours. The mixture was then cooled and evaporated under reduced pressure to dryness. The residue was triturated with ether to give, as a white solid, the title compound, 253 mg, (92%), m.p. 157°.

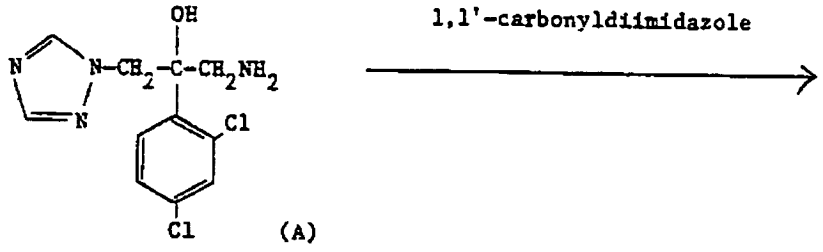
Analysis %:

Found:	C, 45.73;	H, 3.83;	N, 17.78;
Calculated for $C_{12}H_{12}Cl_2N_4O_2$:	C, 45.55;	H, 3.79;	N, 18.09.

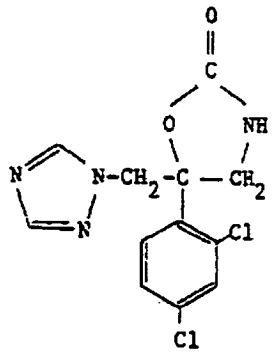
The following Preparations illustrate methods for obtaining certain of the starting materials used in the previous Examples. All temperatures are in °C.

Preparation 1

Preparation of 5-(2,4-dichlorophenyl)-5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



(A)



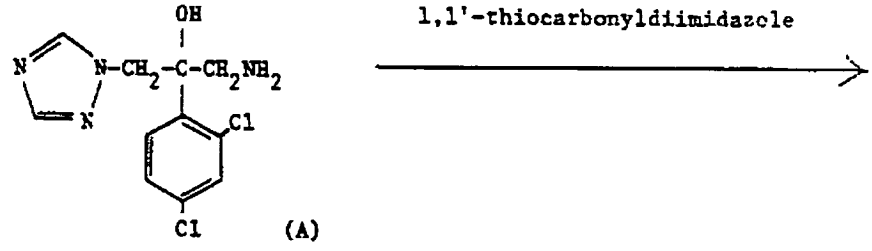
A solution of the amine (A) (0.1 g, 0.35 mmole) and 1,1'-carbonyldiimidazole (0.056 g, 0.35 mmole) in THF (5 ml) was stirred at room temperature for 5 hours. The solvent was then evaporated and the residue was dissolved in ethyl acetate (20 ml). This solution was washed three times with water (300 ml in total), dried ($MgSO_4$), evaporated and the residue triturated with a mixture of 60—80° petrol:ether to give, as a white solid, the *title compound*, 0.074 g (68%), m.p. 223°.

Analysis %:

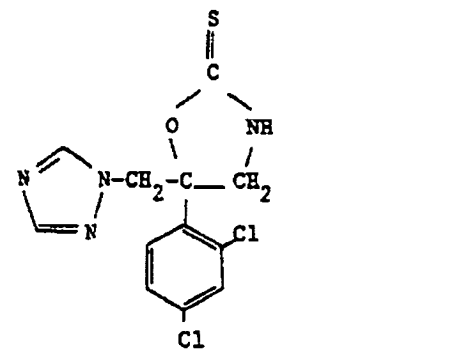
Found:	C, 45.91;	H, 3.27;	N, 18.09;
Calculated for $C_{12}H_{10}Cl_2N_4O_2$:	C, 46.02;	H, 3.22;	N, 17.89.

Preparation 2

Preparation of 5-(2,4-dichlorophenyl)-5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-oxazolidin-2-thione



(A)



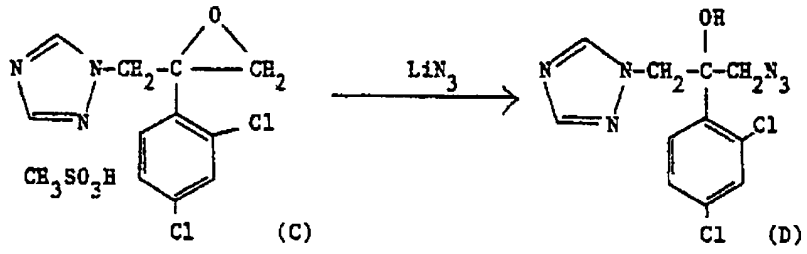
A solution of the amine (A) (1 g, 3.48 mmole) and 1,1'-thiocarbonyldiimidazole (0.62 g, 3.48 mmole) in THF (20 ml) was stirred at room temperature for 1 hour. The solvent was then evaporated and the residue was chromatographed on silica (230—400 mesh), eluting with ethyl acetate to give, after one recrystallisation from ethanol, the *title compound*, 0.65 g, (57%) as a white solid, m.p. 232—235°.

Analysis %:

Found:	C, 43.95;	H, 3.04;	N, 17.37;
Calculated for $C_{12}H_{10}Cl_2N_4OS$:	C, 43.79;	H, 3.06;	N, 17.02.

Preparation 3

Preparation of 1-[3-Azido-2-(2,4-dichlorophenyl)-2-hydroxy-prop-1-yl)-1H-1,2,4-triazole (D)



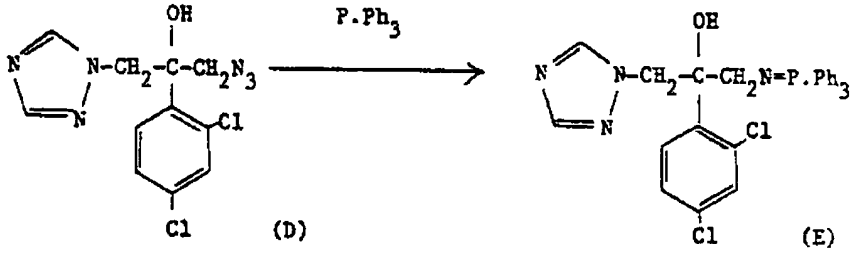
A solution of the epoxide methanesulphonate salt (C) (10 g, 27.32 mmole) and lithium azide (7 g, 143 mmole) in dimethylformamide (100 ml) was stirred at 70° for 1.5 hours. The mixture was then cooled and added to a mixture of dichloromethane (500 ml) and water (50 ml). The organic layer was separated and the aqueous layer was washed a further five times with dichloromethane (200 ml in total). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a colourless gum, trituration of which with ether gave, as a white solid, the *title compound*, 8.2 g (96%), m.p. 119—120°.

Analysis %:

Found:	C, 42,31;	H, 3.23;	N, 27.07;
Calculated for $C_{11}H_{10}Cl_2N_6O$:	C, 42.18;	H, 3.22;	N, 26.83.

Preparation 4

Preparation of N-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-prop-1-yl]triphenylphosphinimine (E)



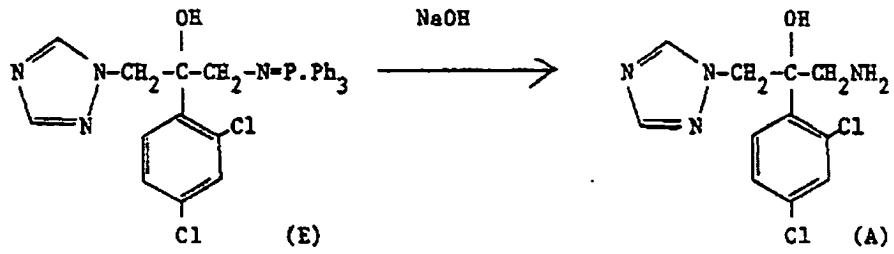
A solution of azide (D) (1 g, 3.2 mmole) and triphenylphosphine (0.84 g, 3.2 mmole) in dichloromethane was stirred at room temperature for 18 hours. Evaporation of solvent and trituration of the residual colourless gum with ether gave, as a white solid, the *title compound*, (1.72 g, 98%), m.p. 183—184°.

Analysis %:

Found:	C, 63.41;	H, 4.59;	N, 10.37;
Calculated for $C_{29}H_{25}Cl_2N_4OP$:	C, 63.6;	H, 4.57;	N, 10.24.

Preparation 5

Preparation of 1-[3-Amino-2-(2,4-dichlorophenyl)-2-hydroxyprop-1-yl]-1H-1,2,4-triazole (A)



A solution of the phosphinimine (E) (0.5 g, 0.914 mmole) in a mixture of methanol (15 ml) and 1N sodium hydroxide solution (5 ml) was heated under reflux for 1.5 hours. The solution was then allowed to cool and the methanol was removed by evaporation under reduced pressure. 3N hydrochloric acid (6 ml) and toluene (10 ml) were then added and the aqueous layer was separated, washed a further three times with toluene (30 ml in total) and then neutralised by addition of solid sodium bicarbonate. Extraction of this solution with dichloromethane (6 × 10 ml), drying ($MgSO_4$) and evaporation of the combined extracts gave, as a white solid, the *title compound*, 254 mg (97%), m.p. 104—105°.

Analysis %:

Found:	C, 45.97;	H, 4.31;	N, 19.26;
Calculated for $C_{11}H_{12}Cl_2N_4O$:	C, 45.99;	H, 4.18;	N, 19.5.

The preferred compounds are the products of Examples 14 to 16 and 20—22, which are especially active as human and plant fungicides. The most preferred individual compounds are the products of Examples 14 and 21.

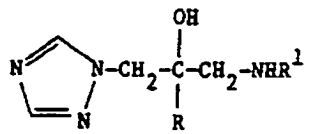
In vivo data (oral PD_{50} values obtained in mice inoculated with *Candida albicans*) for these compounds are as follows:

Product of Example No.	PD_{50} (mg./kg.)
14	1.5
15	4.2
16	3.5
20	4.2
21	1.3
22	2.4

Thus in a preferred aspect R is 2,4-dichlorophenyl and R^1 is —COR^3 where R^3 is 6-chloro-3-pyridyl, isopropyl, *p*-chlorobenzyl, 2,4-dichlorophenyl, 4-chlorophenyl or methyl.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

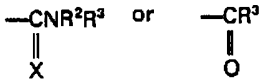
1. A triazole of the formula:



— (I)

or an O-ester or O-ether thereof, said O-ester being a C_2—C_4 alkanoyl or benzoyl ester, said benzoyl ester being optionally substituted by halo, C_1—C_4 alkyl or C_1—C_4 alkoxy, and said O-ether being a C_1—C_6 alkyl, C_2—C_4 alkenyl, C_2—C_4 alkynyl, phenyl or benzyl ether, said benzyl ether being optionally ring-substituted by halo, C_1—C_4 alkyl or C_1—C_4 alkoxy; wherein

R is naphthyl, biphenylyl or phenyl optionally substituted by 1 to 3 substituents each independently selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy; and R^1 is



where

X is O or S;

R^2 is hydrogen or C_1—C_4 alkyl; and

R^3 is (i) hydrogen, (ii) C_1—C_4 alkyl, (iii) C_3—C_6 cycloalkyl, (iv) phenyl optionally substituted by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy; (v) benzyl optionally substituted on the phenyl ring portion by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy or (vi) pyridyl, pyrimidinyl or pyrazinyl all optionally substituted by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl, C_1—C_4 alkoxy and hydroxy; or R^2 and R^3 taken together with the N atom to which they are attached represent a 1-pyrrolidinyl or piperidino group;
or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein R is phenyl substituted by 1 or 2 substituents by 1 or 2 substituents each selected from halo and CF_3.

3. A compound as claimed in claim 2, wherein R is 2,4-dichlorophenyl or 2,4-difluorophenyl.

4. A compound as claimed in claim 1 wherein R is 2,4-dichlorophenyl, and R^1 is —COR^3 where R^3 is 6-chloro-3-pyridyl, isopropyl, p-chlorobenzyl, 2,4-dichlorophenyl, 4-chlorophenyl or methyl.

5. An agriculturally acceptable salt of a compound as claimed in any one of the preceding claims.

6. A pharmaceutical composition comprising a compound of the formula (I) as claimed in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

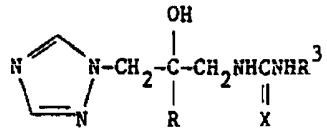
7. A compound of the formula (I) as claimed in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use in treating a fungal infection in a human being.

8. The use of a compound of the formula (I), or an agriculturally acceptable salt thereof, as an agricultural fungicide.

9. An antifungal composition for agricultural use comprising a compound of the formula (I) as claimed in any one of claims 1 to 4, or an agriculturally acceptable salt thereof, together with an agriculturally acceptable diluent or carrier.

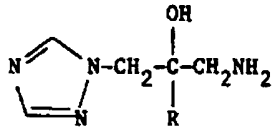
Claims for the Contracting State: AT

1. A process for preparing a triazole antifungal agent of the formula:



--- (IA)

where R is naphthyl, biphenylyl or phenyl optionally substituted by 1 to 3 substituents each independently selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy, R^3 is (i) C_1—C_4 alkyl, (ii) C_3—C_6 cycloalkyl, (iii) phenyl optionally substituted by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy; (iv) benzyl optionally substituted on the phenyl ring portion by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy or (v) pyridyl, pyrimidinyl or pyrazinyl all optionally substituted by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl, C_1—C_4 alkoxy and hydroxy; or R^2 and R^3 taken together with the N atom to which they are attached represent a 1-pyrrolidinyl or piperidino group; and X is O or S; or a pharmaceutically acceptable salt thereof, characterised by reacting a compound of the formula:



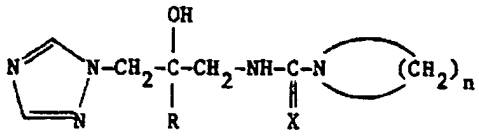
--- (II)

where R is as defined above, with a compound of the formula:

$R^3.NCX$ (III)

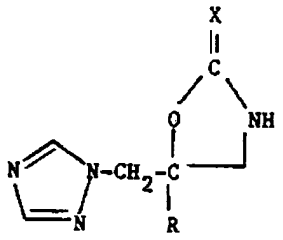
where R^3 and X are as defined above, followed by, optionally, conversion of the product into a pharmaceutically acceptable salt by reaction with a non-toxic acid.

2. A process for preparing a triazole antifungal agent of the formula:



--- (IB)

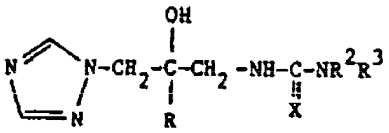
or a pharmaceutically acceptable salt thereof, where R and X are as defined in claim 1 and n is 4 or 5, which comprises reacting a compound of the formula:



--- (IV)

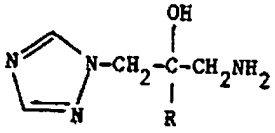
where R and X are as defined in claim 1, with pyrrolidine or piperidine, followed by, optionally, conversion of the product into a pharmaceutically acceptable salt by reaction with a non-toxic acid.

3. A process for preparing a triazole antifungal agent of the formula:



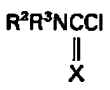
(IC)

or a pharmaceutically acceptable salt thereof, where R and X are as defined in claim 1, R^2 is C_1—C_4 alkyl, and either R^3 is as defined in claim 1, or R^2 and R^3 taken together with the N atom to which they are attached represent a 1-pyrrolidinyl or piperidino group; which comprises reacting a compound of the formula:



--- (II)

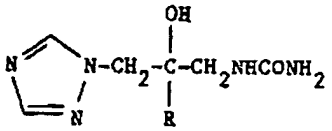
where R is as defined above, with a compound of the formula:



(V)

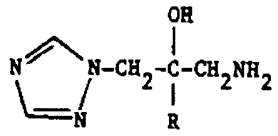
where X, R^2 and R^3 are as defined above, followed by, optionally, conversion of the product into a pharmaceutically acceptable salt by reaction with a non-toxic acid.

4. A process for preparing a triazole antifungal agent of the formula:



--- (ID)

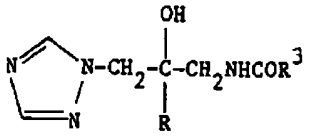
or a pharmaceutically acceptable salt thereof, where R is as defined in claim 1, which comprises reacting a compound of the formula:



--- (II)

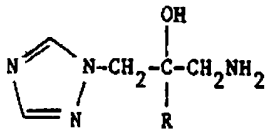
where R is as defined above, with urea; followed by, optionally, conversion of the product into a pharmaceutically acceptable salt by reaction with a non-toxic acid.

5. A process for preparing a triazole antifungal agent of the formula:



--- (IE and IF)

or a pharmaceutically acceptable salt thereof, where R is as defined in claim 1, and R^3 is either H or is as defined in claim 1, which comprises acylating a compound of the formula:



--- (II)

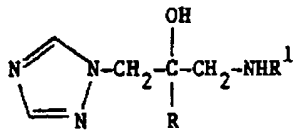
where R is as defined above, with an appropriate acylating agent; followed by, optionally, conversion of the product into a pharmaceutically acceptable salt by reaction with a non-toxic acid.

6. A process as claimed in claim 5, wherein said acylating agent is either (a) a C_1—C_4 alkyl formate, (b) an acid chloride or anhydride of the formula R^3COCl or $(R^3CO)_2O$ where R^3 is as defined in claim 5 except for H, or (c) an acid of the formula R^3COOH where R^3 is as defined in claim 5 except for H, the reaction with said acid being carried out in the presence of 1,1'-carbonyldiimidazole.

7. A process as claimed in any one of the preceding claims, wherein R is phenyl substituted by 1 or 2 substituents each selected from halo and CF_3.

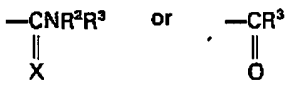
8. A process as claimed in claim 7, where R is 2,4-difluorophenyl or 2,4-dichlorophenyl.

9. A fungicidal composition for agricultural use comprising a diluent or carrier and a compound of the formula:



--- (I)

or an O-ester or O-ether thereof, said O-ester being a C_2—C_4 alkanoyl or benzoyl ester, said benzoyl ester being optionally substituted by halo, C_1—C_4 alkyl or C_1—C_4 alkoxy, and said O-ether being a C_1—C_6 alkyl, C_2—C_4 alkenyl, C_2—C_4 alkynyl, phenyl or benzyl ether, said benzyl ether being optionally ring-substituted by halo, C_1—C_4 alkyl or C_1—C_4 alkoxy; or an agriculturally acceptable salt thereof, wherein R is naphthyl, biphenylyl or phenyl optionally substituted by 1 to 3 substituents each independently selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy; and R^1 is



where

X is O or S;

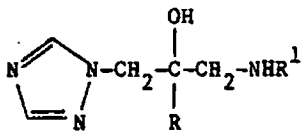
R^2 is hydrogen or C_1—C_4 alkyl; and

R^3 is (i) hydrogen, (ii) C_1—C_4 alkyl, (iii) C_3—C_6 cycloalkyl, (iv) phenyl optionally substituted by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy; (v) benzyl optionally substituted on the phenyl ring portion by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy or (vi) pyridyl, pyrimidinyl or pyrazinyl all optionally substituted by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl, C_1—C_4 alkoxy and hydroxy; or R^2 and R^3 taken together with the N atom to which they are attached represent a 1-pyrrolidinyl or piperidino group.

10. A process for preparing a pharmaceutical composition, characterised by mixing a compound of the formula (I) or an O-ester or O-ether thereof as defined in claim 9, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable diluent or carrier.

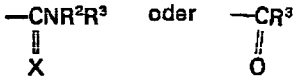
Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Ein Triazol der Formel



--- (I)

oder ein O-Ester oder O-Äther hievon, wobei der O-Ester ein C_2—C_4-Alkanoyl- oder Benzoylester ist, welcher Benzoylester gegebenenfalls mit Halogen, C_1—C_4-Alkyl oder C_1—C_4-Alkoxy substituiert ist, und der O-Äther ein C_1—C_6-Alkyl-, C_2—C_4-Alkenyl-, C_2—C_4-Alkinyl-, Phenyl- oder Benzyläther ist, welcher Benzyläther gegebenenfalls mit Halogen, C_1—C_4-Alkyl oder C_1—C_4-Alkoxy ringsubstituiert ist, worin R Naphthyl, Biphenylyl oder Phenyl gegebenenfalls substituiert mit 1 bis 3 Substituenten jeweils unabhängig ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy bedeutet; und R^1 die Bedeutung



hat, wobei

X O oder S darstellt, R^2 Wasserstoff oder C_1—C_4-Alkyl bedeutet und R (i) Wasserstoff, (ii) C_1—C_4-Alkyl, (iii) C_3—C_6-Cycloalkyl, (iv) Phenyl gegebenenfalls substituiert mit 1 oder 2 Substituenten jeweils unabhängig ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy; (v) Benzyl am Phenylringteil gegebenenfalls substituiert mit 1 oder 2 Substituenten jeweils ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy oder (vi) Pyridyl, Pyrimidinyl oder Pyrazinyl, alle gegebenenfalls substituiert mit 1 oder 2 Substituenten jeweils ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl, C_1—C_4-Alkoxy und Hydroxy ist oder R^2 und R^3 zusammen mit dem N-Atom, an das sie gebunden sind eine 1-Pyrrolidinyl- oder Piperidinogruppe bedeuten, oder ein pharmazeutisch annehmbares Salz hievon.

2. Verbindung, wie in Anspruch 1 beansprucht, worin R Phenyl substituiert mit 1 oder 2 Substituenten jeweils ausgewählt aus Halogen und CF_3 ist.

3. Verbindung, wie in Anspruch 2 beansprucht, worin R 2,4-Dichlorphenyl oder 2,4-Difluorphenyl ist.

4. Verbindung, wie in Anspruch 1 beansprucht, worin R 2,4-Dichlorphenyl und R^1 —COR^3 sind, wobei R^3 6-Chlor-3-pyridyl, Isopropyl, p-Chlorbenzyl, 2,4-Dichlorphenyl, 4-Chlorphenyl oder Methyl bedeutet.

5. Landwirtschaftlich annehmbares Salz einer Verbindung, wie in einem der vorhergehenden Ansprüche beansprucht.

6. Pharmazeutische Zusammensetzung, die eine Verbindung der Formel (I), wie in einem der Ansprüche 1 bis 4 beansprucht, oder ein pharmazeutisch annehmbares Salz hievon zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger umfaßt.

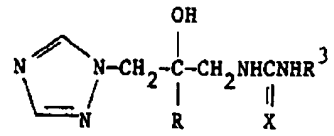
7. Verbindung der Formel (I), wie in einem der Ansprüche 1 bis 4 beansprucht, oder ein pharmazeutisch annehmbares Salz hievon zur Verwendung bei der Behandlung einer Pilzinfektion bei einem Menschen.

8. Verwendung einer Verbindung der Formel (I) oder eines landwirtschaftlich annehmbaren Salzes hievon als landwirtschaftliches Fungizid.

9. Antipilzzusammensetzung zur landwirtschaftlichen Verwendung, die eine Verbindung der Formel (I), wie in einem der Ansprüche 1 bis 4 beansprucht, oder ein landwirtschaftlich annehmbares Salz hievon zusammen mit einem landwirtschaftlich annehmbaren Verdünnungsmittel oder Träger umfaßt.

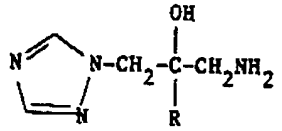
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zum Herstellen eines Triazolantipilzmittels der Formel



--- (IA)

worin R Naphthyl, Biphenylyl oder Phenyl gegebenenfalls substituiert mit 1 bis 3 Substituenten jeweils unabhängig ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy bedeutet, R^3 (i) C_1—C_4-Alkyl, (ii) C_3—C_6-Cycloalkyl, (iii) Phenyl gegebenenfalls substituiert mit 1 oder 2 Substituenten jeweils ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy, (iv) Benzyl gegebenenfalls am Phenylringteil substituiert mit 1 oder 2 Substituenten jeweils ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy oder (v) Pyridyl, Pyrimidinyl oder Pyrazinyl, alle gegebenenfalls substituiert mit 1 oder 2 Substituenten jeweils ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl, C_1—C_4-Alkoxy und Hydroxy ist oder R^2 und R^3 zusammen mit dem N-Atom, an das sie gebunden sind, eine 1-Pyrrolidinyl- oder Piperidinogruppe darstellen, und X O oder S ist, oder eines pharmazeutisch annehmbaren Salzes hievon, gekennzeichnet durch Umsetzen einer Verbindung der Formel



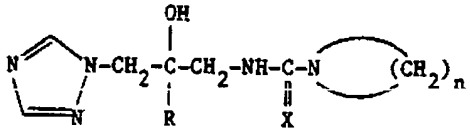
--- (II)

worin R wie oben definiert ist, mit einer Verbindung der Formel

$$R^3 . NCX, \qquad \text{(III)}$$

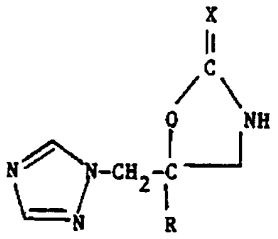
worin R^3 und X wie oben definiert sind, gegebenenfalls gefolgt von der Überführung des Produktes in ein pharmazeutisch annehmbares Salz durch Umsetzen mit einer nicht-toxischen Säure.

2. Verfahren zum Herstellen eines Triazolantipilzmittels der Formel



--- (IB)

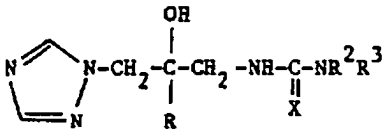
oder eines pharmazeutisch annehmbaren Salzes hievon, worin R und X wie in Anspruch 1 definiert sind und n 4 oder 5 ist, welches das Umsetzen einer Verbindung der Formel



--- (IV)

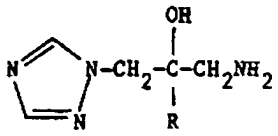
worin R und X wie in Anspruch 1 definiert sind, mit Pyrrolidin oder Piperidin, gegebenenfalls gefolgt von der Überführung des Produktes in ein pharmazeutisch annehmbares Salz durch Umsetzen mit einer nicht-toxischen Säure umfaßt.

3. Verfahren zum Herstellen eines Triazolantipilzmittels der Formel



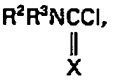
(IC)

oder eines pharmazeutisch annehmbaren Salzes hievon, worin R und X wie in Anspruch 1 definiert sind, R^2 C_1—C_4-Alkyl bedeutet und R^3 entweder wie in Anspruch 1 definiert ist oder R^2 und R^3 zusammen mit dem N-Atom, an das sie gebunden sind, eine 1-Pyrrolidinyl- oder Piperidinogruppe darstellen, welches das Umsetzen einer Verbindung der Formel



— (II)

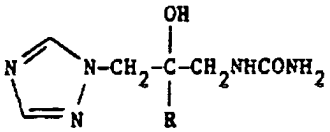
worin R wie oben definiert ist, mit einer Verbindung der Formel



(V)

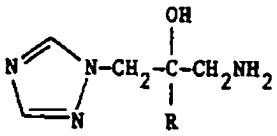
worin X, R^2 und R^3 wie oben definiert sind, gegebenenfalls gefolgt von der Überführung des Produktes in ein pharmazeutisch annehmbares Salz durch Umsetzen mit einer nicht-toxischen Säure umfaßt.

4. Verfahren zum Herstellen eines Triazolantipilzmittels der Formel



--- (ID)

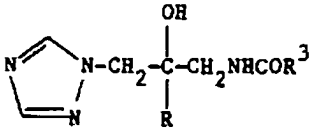
oder eines pharmazeutisch annehmbaren Salzes hievon, worin R wie in Anspruch 1 definiert ist, welches das Umsetzen einer Verbindung der Formel



--- (II)

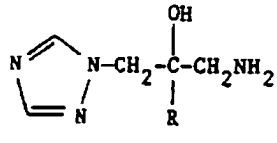
worin R wie oben definiert ist, mit Harnstoff, gegebenenfalls gefolgt von der Überführung des Produktes in ein pharmazeutisch annehmbares Salz durch Umsetzen mit einer nicht-toxischen Säure umfaßt.

5. Verfahren zum Herstellen eines Triazolantipilzmittels der Formel



--- (IE and IF)

oder eines pharmazeutisch annhembaren Salzes hievon, worin R wie in Anspruch 1 definiert ist und R^3 entweder H ist oder wie in Anspruch 1 definiert ist, welches das Acylieren einer Verbindung der Formel



— (II)

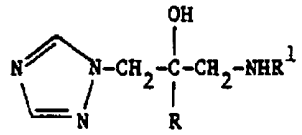
worin R wie oben definiert ist, mit einem geeigneten Acylierungsmittel, gegebenenfalls gefolgt von der Überführung des Produktes in ein pharmazeutisch annehmbares Salz durch Umsetzen mit einer nichttoxischen Säure umfaßt.

6. Verfahren, wie in Anspruch 5 beansprucht, worin das genannte Acylierungsmittel entweder (a) ein C_1—C_4-Alkylformiat, (b) ein Säurechlorid oder -anhydrid der Formel R^3COCl oder $(R^3CO)_2O$, wobei R^3 wie in Anspruch 5 definiert ist, aber ausgenommen H, oder (c) eine Säure der Formel R^3COOH, worin R^3 wie in Anspruch 5 definiert ist, aber ausgenommen H, ist, wobei die Reaktion mit der genannten Säure in Anwesenheit von 1,1'-Carbonyldiimidazol durchgeführt wird.

7. Verfahren, wie in einem der vorhergehenden Ansprüche beansprucht, wobei R Phenyl substituiert mit 1 oder 2 Substituenten jeweils ausgewählt aus Halogen und CF_3 ist.

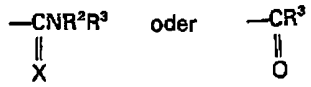
8. Verfahren, wie in Anspruch 7 beansprucht, wobei R 2,4-Difluorphenyl oder 2,4-Dichlorphenyl ist.

9. Fungizide Zusammensetzung zur landwirtschaftlichen Verwendung umfassend ein Verdünnungsmittel oder einen Träger und eine Verbindung der Formel



--- (I)

oder einen O-Ester oder O-Äther hievon, wobei der O-Ester ein C_2—C_4-Alkanoyl- oder Benzoylester ist, welcher Benzoylester gegebenenfalls substituiert ist mit Halogen, C_1—C_4-Alkyl oder C_1—C_4-Alkoxy, und der O-Äther ein C_1—C_6-Alkyl-, C_2—C_4-Alkenyl-, C_2—C_4-Alkinyl-, Phenyl- oder Benzyläther ist, welcher Benzyläther gegebenenfalls mit Halogen, C_1—C_4-Alkyl oder C_1—C_4-Alkoxy ringsubstituiert ist, oder ein landwirtschaftlich annehmbares Salz hievon, worin R Naphthyl, Biphenylyl oder Phenyl gegebenenfalls substituiert mit 1 bis 3 Substituenten jeweils unabhängig ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy bedeutet und R^1 die Bedeutung

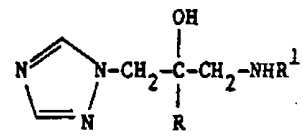


hat, wobei X O oder S ist, R^2 Wasserstoff oder C_1—C_4-Alkyl darstellt, und R^3 (i) Wasserstoff, (ii) C_1—C_4-Alkyl, (iii) C_3—C_6-Cycloalkyl, (iv) Phenyl gegebenenfalls substituiert mit 1 oder 2 Substituenten jeweils ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy, (v) Benzyl gegebenenfalls am Phenylringteil substituiert mit 1 oder 2 Substituenten jeweils ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy oder (vi) Pyridyl, Pyrimidinyl oder Pyrazinyl alle gegebenenfalls substituiert mit 1 oder 2 Substituenten jeweils ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl, C_1—C_4-Alkoxy und Hydroxy ist oder R^2 und R^3 zusammen mit dem N-Atom, an das sie gebunden sind, eine 1-Pyrrolidinyl- oder Piperidinogruppe darstellen.

10. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung, gekennzeichnet durch Mischen einer Verbindung der Formel (I) oder eines O-Esters oder O-Äthers hievon, wie in Anspruch 9 definiert, oder eines pharmazeutisch annehmbaren Salzes hievon mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Triazole de formule:



--- (I)

ou un O-ester ou O-éther de ce composé, ledit O-ester étant un ester d'alcanoyle en C_2 à C_4 ou de benzoyle, ledit ester de benzoyle étant facultativement substitué par un radical halogéno, alkyle en C_1 à C_4 ou alkoxy en C_1 à C_4 et ledit O-éther étant un éther d'alkyle en C_1 à C_6, d'alcényle en C_2 à C_4, d'alcynyle en C_2 à C_4 de phényle ou de benzyle, ledit éther de benzyle étant facultativement substitué sur le noyau par un radical halogéno, alkyle en C_1 à C_4 ou alkoxy en C_1 à C_4; formule dans laquelle R est un groupe naphtyle, biphénylyle ou phényle facultativement substitué par 1 à 3 substituants choisis chacun, indépendamment, entre des substituants halogéno, CF_3, alkyle en C_1 à C_4 et alkoxy en C_1 à C_4; et R^1 représente

$-CNR^2R^3$ (X) ou $-CR^3$ (O)

où

X représente O ou S;

R^2 est l'hydrogène ou un groupe alkyle en C_1 à C_4; et

R^3 représente (i) l'hydrogène, (ii) un groupe alkyle en C_1 à C_4, (iii) un groupe cycloalkyle en C_3 à C_6, (iv) un groupe phényle facultativement substitué par un ou deux substituants choisis chacun entre des radicaux halogéno, CF_3, alkyle en C_1 à C_4 et alkoxy en C_1 à C_4; (v) un groupe benzyle facultativement substitué sur le noyau phényle par un ou deux substituants choisis chacun entre des radicaux halogéno, CF_3, alkyle en C_1 à C_4 et alkoxy en C_1 à C_4, ou bien (vi) un groupe pyridyle, pyrimidinyle ou pyrazinyle tous facultativement substitués par 1 ou 2 substituants choisis chacun entre des radicaux halogéno, CF_3, alkyle en C_1 à C_4, alkoxy en C_1 à C_4 et hydroxy; ou bien R^2 et R^3, pris conjointement avec l'atome d'azote auquel ils sont attachés, représentent un groupe 1-pyrrolidinyle ou pipéridino; ou un sel pharmaceutiquement acceptable de ce composé.

2. Composé suivant la revendication 1, dans lequel R est un groupe phényle substitué par 1 ou 2 substituants choisis tous deux entre des radicaux halogéno et CF_3.

3. Composé suivant la revendication 2, dans lequel R est un groupe 2,4-dichlorophényle ou 2,4-difluorophényle.

4. Composé suivant la revendication 1, dans lequel R est un groupe 2,4-dichlorophényle et R^1 est un groupe $-COR^3$ où R^3 est un radical 6-chloro-3-pyridyle, isopropyle, p-chlorobenzyle, 2,4-dichlorophényle, 4-chlorophényle ou méthyle.

5. Sel acceptable en agriculture d'un composé suivant l'une quelconque des revendications précédentes.

6. Composition pharmaceutique comprenant un composé de formule (I) suivant l'une quelconque des revendications 1 à 4 ou un sel pharmaceutiquement acceptable de ce composé, en association avec un diluant ou support acceptable du point de vue pharmaceutique.

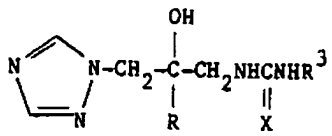
7. Composé de formule (I) suivant l'une quelconque des revendications 1 à 4, ou un sel pharmaceutiquement acceptable de ce composé, destiné à être utilisé dans le traitement d'une infection fongique chez un être humain.

8. Utilisation d'un composé de formule (I) ou d'un sel acceptable en agriculture de ce composé comme fongicide pour l'agriculture.

9. Composition antifongique destinée à être utilisée en agriculture, comprenant un composé de formule (I) suivant l'une quelconque des revendications 1 à 4 ou un sel acceptable en agriculture de ce composé, en association avec un diluant ou support acceptable en agriculture.

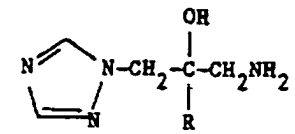
Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un agent antifongique triazolique de formule:



--- (IA)

dans laquelle R est un groupe naphtyle, biphénylyle ou phényle éventuellement substitué par 1 à 3 substituants choisis chacun indépendamment entre des substituants halogéno, CF_3, alkyle en C_1 à C_4 et alkoxy en C_1 à C_4, R^3 représente (i) un groupe alkyle en C_1 à C_4, (ii) un groupe cycloalkyle en C_3 à C_6, (iii) un groupe phényle éventuellement substitué par 1 ou 2 substituants tous deux choisis entre des substituants halogéno, CF_3, alkyle en C_1 à C_4 et alkoxy en C_1 à C_4; (iv) un groupe benzyle éventuellement substitué sur le noyau phényle par 1 ou 2 substituants tous deux choisis entre des substituants halogéno, CF_3, alkyle en C_1 à C_4 et alkoxy en C_1 à C_4 ou (v) un groupe pyridyle, un groupe pyrimidinyle ou un groupe pyrazinyle, tous facultativement substitués par 1 ou 2 substituants choisis chacun entre des substituants halogéno, CF_3, alkyle en C_1 à C_4, alkoxy en C_1 à C_4 et hydroxy; ou bien R^2 et R^3 forment, conjointement avec l'atome d'azote auquel ils sont attachés, un groupe 1-pyrrolidinyle ou pipéridino; et X représente O ou S; ou d'un sel pharmaceutiquement acceptable de ce composé, caractérisé en ce qu'il consiste à faire réagir un composé de formule:



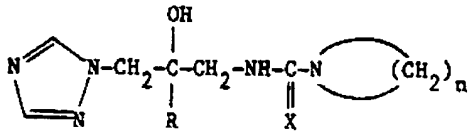
--- (II)

dans laquelle R a la définition donnée ci-dessus, avec un composé de formule:

$$R^3 . NCX \qquad (III)$$

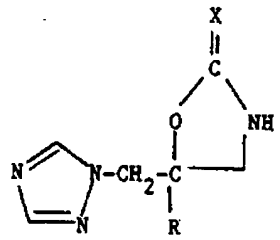
dans laquelle R^3 et X sont tels que définis ci-dessus, la réaction étant suivie, facultativement, de la transformation du produit en un sel pharmaceutiquement acceptable par réaction avec un acide non toxique.

2. Procédé de préparation d'un agent antifongique triazolique de formule:



--- (IB)

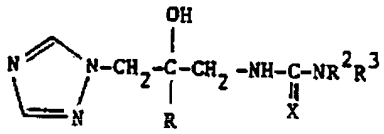
ou d'un sel pharmaceutiquement acceptable de ce composé, formule dans laquelle R et X sont tels que définis dans la revendication 1 et *n* a la valeur 4 ou 5, qui consiste à faire réagir un composé de formule:



--- (IV)

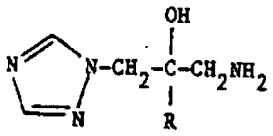
dans laquelle R et X sont tels que définis dans la revendication 1, avec la pyrrolidine ou la pipéridine, la réaction étant suivie, facultativement, de la transformation du produit en un sel pharmaceutiquement acceptable par réaction avec un acide non toxique.

3. Procédé de préparation d'un agent antifongique triazolique de formule:



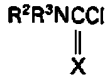
(IC)

ou d'un sel pharmaceutiquement acceptable de ce composé, formule dans laquelle R et X sont tels que définis dans la revendication 1, R^2 est un groupe alkyle en C_1 à C_4 et R^3 a la définition donnée dans la revendication 1, ou bien R^2 et R^3 forment, conjointement avec l'atome d'azote auquel ils sont liés, un groupe 1-pyrrolidinyle ou pipéridino; procédé qui consiste à faire réagir un composé de formule:



--- (II)

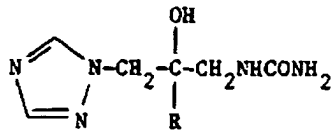
dans laquelle R a la définition donnée ci-dessus, avec un composé de formule:



(V)

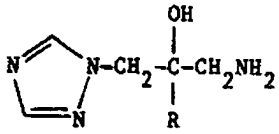
dans laquelle X, R^2 et R^3 sont tels que définis ci-dessus, la réaction étant suivie, facultativement, de la transformation du produit en un sel pharmaceutiquement acceptable par réaction avec un acide non toxique.

4. Procédé de préparation d'un agent antifongique triazolique de formule:



--- (ID)

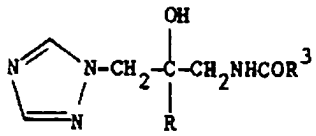
ou d'un sel pharmaceutiquement acceptable de ce composé, formule dans laquelle R a la définition donnée dans la revendication 1, qui consiste à faire réagir un composé de formule:



--- (II)

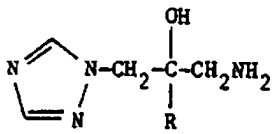
dans laquelle R a la définition donnée ci-dessus, avec l'urée; la réaction étant suivie, facultativement, de la transformation du produit en un sel pharmaceutiquement acceptable par réaction avec un acide non toxique.

5. Procédé de préparation d'un agent antifongique triazolique de formule:



--- (IE and IF)

ou d'un sel pharmaceutiquement acceptable de ce composé formule dans laquelle R a la définition donnée dans la revendication 1 et R^3 représente H ou a la définition donnée dans la revendication 1; procédé qui consiste à acyler un composé de formule:



--- (II)

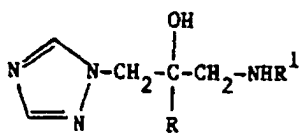
dans laquelle R a la définition donnée ci-dessus, avec un agent acylant appropriée; la réaction étant suivie, facultativement, de la transformation du produit en un sel pharmaceutiquement acceptable par réaction avec un acide non toxique.

6. Procédé suivant la revendication 5, dans lequel l'agent acylant est (a) un formiate d'alkyle en C_1 à C_4, (b) un chlorure ou anhydride d'acide de formule R^3COCl ou $(R^3CO)_2O$ dans laquelle R^3 a la définition donnée dans la revendication 5 hormis un atome d'hydrogène, ou bien (c) un acide de formule R^3COOH dans laquelle R^3 a la définition donnée dans la revendication 5 hormis un atome d'hydrogène, la réaction avec ledit acide étant conduite en présence de 1,1'-carbonyldiimidazole.

7. Procédé suivant l'une quelconque des revendications précédentes, dans lequel R est un groupe phényle substitué par 1 ou 2 substituants tous deux choisis entre des radicaux halogéno et CF_3.

8. Procédé suivant la revendication 7, dans lequel R est un groupe 2,4-difluorophényle ou 2,4-dichlorophényle.

9. Composition fongicide destinée à l'agriculture, comprenant un diluant ou support et un composé de formule:



--- (I)

ou un O-ester ou O-éther de ce composé, ledit O-ester étant un ester d'alcanoyle en C_2 à C_4 ou de benzoyle,

ledit ester de benzoyle étant facultativement substitué par un radical halogéno, alkyle en C_1 à C_4 ou alkoxy en C_1 à C_4 et ledit O-éther étant un éther d'alkyle en C_1 à C_6, d'alcényle en C_2 à C_4, d'alcynyle en C_2 à C_4, de phényle ou de benzyle, ledit éther de benzyle étant facultativement substitué sur le noyau par un radical halgéno, alkyle en C_1 à C_4 ou alkoxy en C_1 à C_4; ou un sel acceptable en agriculture de ce composé, formule dans laquelle R est un groupe naphtyle, biphénylyle ou phényle facultativement substitué par 1 à 3 substituants choisis, indépendamment, entre des substituants halogéno, CF_3, alkyle en C_1 à C_4 et alkoxy en C_1 à C_4; et R^1 représente

$$-C(=X)NR^2R^3 \quad \text{ou} \quad -C(=O)R^3$$

où

X représente O ou S;

R^2 est l'hydrogène ou un groupe alkyle en C_1 à C_4; et

R^3 représente (i) l'hydrogène, (ii) un groupe alkyle en C_1 à C_4, (iii) un groupe cycloalkyle en C_3 à C_5, (iv) un groupe phényle facultativement substitué par 1 ou 2 substituants tous deux choisis entre des radicaux halogéno, CF_3, alkyle en C_1 à C_4 et alkoxy en C_1 à C_4; (v) un groupe benzyle facultativement substitué sur le noyau phényle par 1 ou 2 substituants tous deux choisis entre des substituants halogéno, CF_3, alkyle en C_1 à C_4 et alkoxy en C_1 à C_4, ou bien (vi) un groupe pyridyle, un groupe pyrimidinyle ou un groupe pyrazinyle, tous facultativement substitués par 1 ou 2 substituants choisis chacun entre des radicaux halogéno, CF_3, alkyle en C_1 à C_4, alkoxy en C_1 à C_4 et hydroxy; ou bien R^2 et R^3 forment, conjointement avec l'atome d'azote auquel ils sont liés, un groupe 1-pyrrolidinyle ou pipéridino.

10. Procédé de préparation d'une composition pharmaceutique, caractérisé par le mélange d'un composé de formule (I) ou d'un O-ester ou d'un O-éther de ce composé tel que défini dans la revendication 9, ou d'un sel pharmaceutiquement acceptable de ce composé, avec un diluant ou support acceptable du point de vue pharmaceutique.